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Autoimmune Thyroid Diseases in 65 Japanese Women with Turner Syndrome

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Abstract. Turner syndrome (TS) is associated with a number of complications including thyroid disease. In this study, the prevalence of thyroid disease was evaluated in Japanese women with TS. The medical charts of 65 TS women (age 30±9 years old, range: 15-61), treated with estrogen replacement therapy or with antiosteoporotic pharmaceuticals at our outpatient clinic, were reviewed. History of thyroid disease, titer of thyroid autoantibodies and thyroid function were recorded. Thyroid autoantibodies were undetectable in 28 of 65 women (43%), and thyroid function was normal in all these women. Of the 37 women with thyroid autoantibodies (57%), 3 had Graves' disease and 20 women were hypothyroidism and diagnosed as Hashimoto's thyroiditis. The remaining 14 women with euthyroidism were also considered to be so-called probable cases of Hashimoto's thyroiditis. In 20 women with hypothyroidism, 14 (70%) received replacement therapy with levothyroxine. The replacement with levothyroxine started between age 17 and 60 (median: 31 years old). These data showed that more than half of Japanese women with TS in adulthood had thyroid autoantibodies. In women with TS, monitoring of thyroid hormone is important to detect hypothyroidism earlier and start adequate replacement therapy.

Key words: Hashimoto's thyroiditis, Turner syndrome

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TURNER SYNDROME is a relatively common chromosomal disorder, caused by complete or partial X monosomy in some or all cells. This syndrome is characterized by short stature and estrogen deficiency secondary to ovarian dysgenesis. Affected women are susceptible to a number of medical problems including cardiovascular disease, osteoporosis, and other endocrine disorders [1]. A high prevalence of autoimmune thyroid disease has been also described in Turner syndrome [1], but only a few surveys of Japanese women with Turner syndrome have been reported. Several previous studies showed that hypothyroidism began to appear even before adolescence in Turner syndrome [1]. In the general population, the prevalence of overt and subclinical hypothyroidism increases with age [2]. The incidence of thyroid disease apparently increases with age as well in women with Turner syndrome. In this study, we analyzed the prevalence of thyroid disease associated with Turner syndrome in adulthood in Japan.

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Subjects and Methods

The medical charts of 65 women with Turner syndrome (age mean±SD: 30±9 yr. range; 15-61) who were attending our outpatient clinic to receive estrogen replacement therapy or antiosteoporotic pharmaceuticals, were retrospectively reviewed. The diagnosis of Turner syndrome was based on clinical findings such as short stature, primary amenorrhea and cubitus valgus *etc.*, and peripheral blood leukocyte karyotype analysis. The karyotype was 45X in 20 women, isochromosome-X (including 46XiX(q), 45X/46XiX(q), 45X/46Xi(X)(q10)) in 20, structural disturbances in 13, mosaic without structural disturbances (including 45X/46XX, 45X/ 47XXX) in 4. In 8 women, the

precise karyotype data was unknown as it was not described in a referral from former doctors. Two women had a family history of thyroid disease and there were two smokers. Each patient was screened for thyroid abnormalities by clinical examination and laboratory evaluation, including evaluation of thyroid function and thyroid autoantibodies. Measurements of thyrotropin (TSH), free T_3, free T_4, thyroglobulin autoantibodies, and autoantibodies to thyroid peroxidase or antimicrosomal autoantibodies were performed using standard hospital laboratory techniques. Autoantibody to TPO and thyroglobulin were measured by solid-phase RIA (Cosmic Corp., Tokyo, Japan, normal range less than 0.3 U/mL, respectively) or by hemagglutination methods (Serodia ATG and TG, Tokyo, Japan, normal range less than 100, respectively). The diagnosis of Hashimoto's thyroiditis was based on the guideline determined by Japan Thyroid Association.

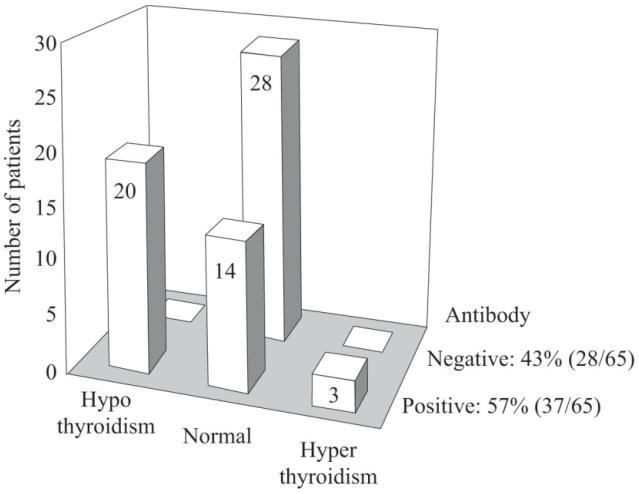

Fig. 1 Thyroid function and thyroid autoantibodies in 65 patients with Turner syndrome.
The numerals in the columns mean the number of patients.

Results

Twenty-eight of 65 women (43%) had no thyroid autoantibodies. Their thyroid function was normal. The remaining 37 (57%) women had either thyroglobulin autoantibodies or autoantibodies to thyroid peroxidase (Fig. 1). Twenty-three women had both autoantibodies, other women had either an autoantibody to thyroglobulin (n=8) or to thyroid peroxidase (n=6), respectively. Of the 37 women positive for thyroid autoantibodies, the numbers of the women with hyperthyroidism, hypothyroidism and normal thyroid function were 3, 20 and 14, respectively (Fig. 1). Three women with hyperthyroidism had Graves' disease (age at onset: 11, 27, and 28 years, respectively). Twenty women with hypothyroidism were considered to have Hashimoto's thyroiditis. The 14 of 20 women were treated with levothyroxine beginning at the median age of 31 (range: 17-60 years old), while the remaining 6 women were left untreated with levothyroxine. When levothyroxine was started, serum fT_3 and/or fT_4 levels decreased less than the lower limit of the reference range in 6 women and sustained elevation of serum TSH levels with normal fT_3 and fT_4 levels was observed in 8 women (TSH levels between 6 and 10 μU/mL in 4, more than 10 μU/mL in 4, respectively).

Fourteen women positive for thyroid autoantibodies had normal thyroid function (Fig. 1). Thyroid ultrasonography was performed in 7 of these 14 women. The findings of Hashimoto's thyroiditis were revealed in 5 women. In other 9 women including two with normal findings by thyroid ultrasonography, the presence of goiter was not recorded in the medical chart. These women were considered to be so-called probable cases of Hashimoto's thyroiditis.

Figure 2 shows the numbers of women who had thyroid autoantibodies in each decade. Fifty-two percent of women under 40 years old (29/56) had thyroid autoantibodies. On the other hand, 89% of the women above 40 years old (8/9) had thyroid autoantibodies.

Discussion

In this study, more than half of the adults with Turner syndrome had thyroid autoantibodies, and the prevalence of hypothyroidism was 31% (20/65). Seventy percent of the women with hypothyroidism were receiving L-thyroxine. In 1993, Konno *et al*. investigated the prevalence of thyroid dysfunction and its relation to thyroid autoantibodies in apparently healthy people residing in Japan [3]. They reported that the thyroid autoantibodies were positive in 13.8% of females. There was an age-related increase in the prevalence of positive thyroid autoantibodies and the frequency was about 7% below 30 years old, and 14% above 30 years of age. The overall preva-

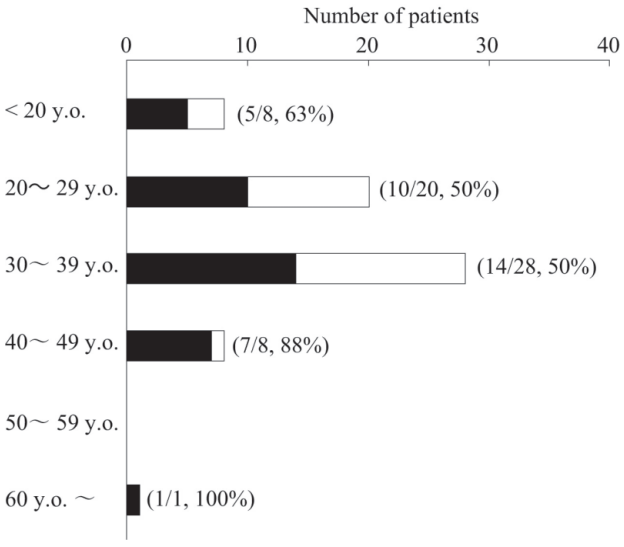

Fig. 2 The numbers of patients with Turner syndrome who have thyroid autoantibody in each decade.
Black columns: autoantibody positive; white columns: autoantibody negative. The numbers in parenthesis represent the positive rate of thyroid autoantibody.

lence of Hashimoto's thyroiditis in females in the general Japanese population was 13%. By comparison, the prevalence of positive thyroid autoantibodies was high in Japanese women with Turner syndrome in this study. In previous reports from European countries, the incidence of thyroiditis in girls with Turner syndrome was between 10% and 24% [4-6]. The frequency of thyroid abnormalities increases with age in Turner syndrome as well as in the general population. The incidence of hypothyroidism due to Hashimoto's thyroiditis in adults with Turner syndrome was reported as 16-30% [1, 4, 7-9]. In 2005, El-Mansoury *et al*. reported that the prevalence of hypothyroidism in Swedish adults with Turner syndrome was 25% in a large cohort study [8]. Moreover, after the 5-yr follow up, the incidence became up to 37% in this Swedish study [8]. In our series in Japan, the incidence of hypothyroidism (31%) was nearly the same values as those reported in the literature.

The reason for the higher prevalence of autoimmune thyroid disease in Turner syndrome is unknown. One hypothesis is that the X chromosomal anomaly associated with this syndrome might play an important pathogenetic role in the development of autoimmune disease, as the prevalence of other immune-mediated diseases such as inflammatory bowel disease is also high in Turner syndrome [1].

Elsheikh *et al*. reported that autoimmune thyroid disease has been found to be particularly prevalent in women with the isochromosome karyotype compared with other karyotypes [1]. In this study, 9 of 20 women with 45X (45%) and 13 of 20 women with the isochromosome (65%) had thyroid autoantibodies and the prevalence was not statistically significant by chi-square test for independence.

Recently, Hamano *et al*. assessed the arterial stiffness of patients with hypothyroidism by the brachial-ankle pulse wave velocity and found that an early atherosclerosis process was observed not only in overt but also in subclinical hypothyroidism, and this process could be reversed by an appropriate hormone replacement therapy [10]. Taking these findings into consideration, thyroid function in women with Turner syndrome should be monitored repeatedly to avoid unrecognized hypothyroidism.

In this study, 3 of 65 women had Graves' disease. Our findings were consistent with the earlier findings that Graves' disease may occur in women with Turner syndrome, although the incidence was low [5]. In line with earlier studies, we observed that Hashimoto's thyroiditis was the most frequent type of thyroid dysfunction in women with Turner syndrome.

In this series, all women negative for thyroid autoantibody had normal thyroid function. However, Massa *et al*. indicated that some women without detectable antithyroid antibody had goiter or biochemical hypothyroidism and that the absence of thyroid autoantibody did not exclude a disturbance of thyroid function [11]. Therefore, it would be important to survey the thyroid function of these women with Turner syndrome regularly even if they were negative for thyroid autoantibody.

In conclusion, more than half of women with Turner syndrome in adulthood had thyroid autoantibodies. Thyroid function in women with Turner syndrome should be monitored repeatedly to avoid unrecognized hypothyroidism and start adequate replacement therapy with levothyroxine promptly.

Acknowledgements

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